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Risk of pneumonia in patients taking statins:

population-based nested case–control study

Abstract

Background
Community-acquired pneumonia is one of the most common causes of hospitalisation and death in older people. Recent research suggests that statins might improve the outcome of infectious diseases because of their anti-oxidative and anti-inflammatory properties.

Aim
To estimate the association between current statin use and the risk of community-acquired pneumonia.

Design and setting
Nested case–control study of 443 general practices in the UK within the QResearch® database.

Method
Individuals with newly recorded pneumonia, diagnosed between 1996 and 2006 and aged 45 years and older, were matched with up to five controls by age, sex, general practice, and calendar year. Odds ratios for pneumonia associated with statin use were adjusted for smoking status, deprivation, comorbidities, use of acid-lowering drugs, influenza, and pneumococcal vaccines.

Results
The analysis found a decreased risk of pneumonia in patients prescribed statins in the year prior to diagnosis (adjusted odds ratio = 0.78, 95% confidence interval [CI] = 0.74 to 0.83), particularly in patients with prescriptions in the last 28 days (adjusted odds ratio = 0.68, 95% CI = 0.63 to 0.73). Atorvastatin and simvastatin had similar associations with pneumonia risk. Analysis repeated on lobar and pneumococcal pneumonia cases showed comparable results.

Conclusion
In this large population-based case–control study, current exposure to statins was associated with a reduced risk of pneumonia. The findings were similar to other observational population-based studies, but further randomised controlled trials are necessary before recommending statins to patients at high risk of pneumonia.

Keywords
general practice; pneumonia; statins; population.

INTRODUCTION

Community-acquired pneumonia is one of the most common causes of hospitalisation and death in older people.[1–3] The annual incidence of pneumonia is around 230 patients per 100 000 person-years and varies by age group, being highest in patients aged 60 years or older (670 per 100 000).[4] A large number of the adult population are prescribed statins for prevention and treatment of cardiovascular disease,[5,6] accounting for 11% of the general population in the UK aged 30–84 years.[7]

Laboratory data suggest that statins improve the outcome of infectious diseases because of their anti-oxidative and anti-inflammatory properties.[8] *Chlamydia pneumoniae* infection stimulates chronic inflammation in vascular cells, and this has been shown to be reduced in vitro by statin administration.[9] Another study demonstrated the ability of rosuvastatin to attenuate the inflammatory process by inhibiting endothelial cell adhesion molecule expression.[10] One review illustrated that statin types have their own immunomodulatory properties[11] and, therefore, that their effect on inflammatory processes might vary. A laboratory study demonstrated a significant reduction of leukocyte counts in septic mice treated with atorvastatin compared to other statins and placebo.[12] Another laboratory study, on blood culture, showed an antimicrobial effect for simvastatin,[13] but not for fluvastatin, with a possible explanation related to the difference in origin of these two statins: fungal fermentation and chemical synthesis respectively.

A few prospective cohort studies[14–17] have investigated statin use in relation to pneumonia and found an association between statin use and decreased risk of mortality or severe sepsis.[14] However, a Canadian study based on 3415 patients with pneumonia showed no reduction in mortality or need for admission to intensive care among statin users.[18] A few case–control studies have investigated the effect of statin use on the risk of community-acquired pneumonia,[19–22] but none of them looked at the effect of specific statin types.

One study in people aged 30 years and older found a reduction in pneumonia risk in patients currently taking statins, but this was significant only in fatal pneumonia.[19] Another study, in patients with diabetes, showed a beneficial role of statins in reducing fatal/non-fatal pneumonia.[20] A case–control study conducted on the general population showed a 22% reduction of pneumonia risk in patients on statins.[21] However, a recent population-based case–control study in older people did not demonstrate a beneficial effect from current statin use.[22]

As these studies have found conflicting results, and have not looked at different types of statins, a case–control study was performed using the QResearch® primary care database to estimate the effect of current exposure to statins, including the most common types, on the risk of

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How this fits in

There is evidence that statins improve the outcome of infectious diseases because of their anti-oxidative and anti-inflammatory properties. A number of studies have investigated the association between statins and risk of pneumonia, and arrived at different conclusions. This study found that statin use was associated with a decreased risk of pneumonia, particularly in patients prescribed a statin in the last 28 days (odds ratio = 0.68, 95% confidence interval = 0.63 to 0.73). Simvastatin and atorvastatin appeared to have similar associations with the risk of pneumonia.

community-acquired pneumonia.

METHOD

Study design and data source

These analyses used data from a previous population-based nested case–control study of identification of new risk factors for pneumonia.[23] It was conducted within a cohort of patients registered between 1 January 1996 and 31 December 2005 with practices in the UK contributing to the QResearch database (downloaded August 2006, http://www.qresearch.org). This database gathers anonymised information from more than 500 UK general practices using the Egton Medical Information Systems clinical computer system, and contains patient demographics, characteristics, clinical diagnoses, and prescribed medications including repeat prescriptions. The consenting practices form a representative sample of 6% of all UK general practices.[24] The database has been validated by comparing birth rates, death rates, consultation rates, prevalence, and mortality rates with other data sources including the General Household Survey, the General Practice Research Database, and prevalence data from the new General Medical Services contract for GPs.

Study population

The study selected all patients aged 45 years and older and identified newly recorded cases of pneumonia from diagnostic Read codes in the patient records (a list of codes for all diagnoses in the paper is available from the authors) occurring during the 10-year study period, including those with a post mortem diagnosis. Patients with a diagnosis of pneumonia prior to their entry into the cohort, and those with fewer than 2 years of electronic health records were excluded to increase the completeness of data. Each case was linked to five controls, which were randomly selected from those alive and registered with the practice at the time of the case's diagnosis (index date), and matched on age (to within 1 year), sex, practice, and calendar year.

Assessment of exposure

The study focused on exposure to statins in the year prior to the index date, analysing prescription information related to this period of time and considering a patient as a statin user if they had at least two prescriptions for any statin, with the last one issued during the last year prior to the index date.

The recency of statin prescriptions was also studied. As general practices usually prescribe these medications for 28 days' duration, a prescription issued in the last 28 days prior to the index date should reflect current statin use at the index date. Therefore, the time since the last prescription before the index date was coded as follows: within the last 28 days; in the previous 29–89 days; in the previous 90–365 days; not prescribed within the last 12 months.

The study also investigated associations with each type of statin (atorvastatin, fluvastatin, pravastatin, cerivastatin, rosuvastatin, and simvastatin) prescribed at least twice, with the last prescription issued in the last year before the index date. For the most common types of statin — atorvastatin and simvastatin — time since the last prescription was also categorised as described above.

Confounding factors

The analyses were adjusted for current smoking status (smoker, non-smoker) and for socioeconomic deprivation, using the Townsend score (in fifths) based on 2001 postcode-related census data.

As they are conditions identified in UK pneumococcal vaccine guidelines, the analysis also used diagnostic Read codes in the patient records to adjust for the following morbidities if they were diagnosed prior to the index date: diabetes; chronic heart disease; chronic renal disease; chronic respiratory disease; asplenia; cerebrospinal fluid shunt; chronic liver disease; sickle cell disease; coeliac disease; cochlear implant; HIV/AIDS; or immunosuppression. As they also affect the risk of pneumonia, the following additional risk factors were considered if they were diagnosed prior to the index date: stroke or transient ischaemic attack; rheumatoid arthritis; Parkinson's disease; cancers; multiple sclerosis; dementia; and osteoporosis.[23]

Other medications and vaccinations were adjusted for if they were prescribed in the 12 months before the index date. These included acid-lowering drugs (proton pump inhibitors and H_2-receptor antagonists, at least one prescription) because of the increased risk of pneumonia,[25,26] and influenza vaccinations and pneumococcal vaccinations, as they may be associated with a decreased risk of pneumonia.[27]

Statistical analysis

Conditional logistic regression was used for individually matched case–control studies, to derive odds ratios with 95% CIs for the risk of pneumonia associated with statin exposure, unadjusted and adjusted for the potential confounding factors listed previously. Missing values for smoking status and Townsend score were analysed as separate categories. Key analyses were repeated, restricted to cases with lobar and pneumococcal pneumonia and their controls, because those diagnoses were most likely made on hospital discharge and therefore confirmed by X-ray or microbiological tests.

A 1% significance level was chosen to account for multiple comparisons. STATA (version 10) was used.

As this study analysed data that had been extracted for another study,[23] the sample size was not calculated before the study. However, to detect an odds ratio of 0.8 with 80% power at 1% significance for an exposure that occurs in 4.2% of controls (atorvastatin), a sample size of 8085 cases would be needed. There were sufficient observations to investigate the effect of different types of statin and to analyse the recency of use for the most common statins (atorvastatin and simvastatin), but the study was underpowered to investigate the effect of recency of exposure to the common statins in cases with pneumococcal and lobar pneumonia and their controls.

Sensitivity analysis

As patients with particularly bad health might be at higher risk of pneumonia but less likely to be treated with statins, the analysis was repeated excluding patients receiving immunosuppressive drugs and those diagnosed with cancer, HIV/AIDS, or chronic kidney disease. As the proportion of missing values in smoking status records differed between cases and controls, the analysis was repeated on cases and controls with complete data for smoking status and deprivation.

RESULTS

Overall, there were 22 498 cases aged 45 years and older with a newly recorded diagnosis of pneumonia from 443 QResearch general practices within the study period: an overall crude rate of 194 per 100 000 person-years. After excluding 4727 cases with less than 2 years of medical records, 17 755 cases and 80 484 controls were analysed. Fifty-one per cent of cases were females, and the median age of the cases was 74 years (interquartile range 62–82 years). Cases were more likely than controls to live in deprived areas, to be current smokers, and to have comorbidities. Table 1 shows frequencies and adjusted odds ratios associated with risk of pneumonia for patient characteristics, comorbidities, and some medications and vaccinations when all those factors were included into the multivariable model. Seventy-six per cent of cases and 65% of controls had complete data for smoking status and deprivation score. There were differences in observed characteristics between those with and without missing data, supporting the assumption that data are missing at random.

Table 2 shows the results for statin exposure in the year before the index date. Although cases were more likely to have been prescribed statins overall (unadjusted odds ratio = 1.24, 95% CI = 1.18 to 1.31), after adjusting for comorbidities there was a 19% decreased risk of pneumonia associated with statin prescriptions (adjusted odds ratio = 0.81, 95% CI = 0.76 to 0.85) and a 22% decreased risk after adjusting for all confounding factors (adjusted odds ratio = 0.78, 95% CI = 0.74 to 0.83). This would be equivalent to an absolute risk reduction of 4 (95 % CI = 3 to 5) cases per 10 000 patients aged 45 years and older treated over 1 year, assuming a causal association. Among patients prescribed statins in the last year, 54.8% of cases and 62.2% of controls had a prescription issued in the last 28 days before the index date. For these current statin users, there was a 9% unadjusted increased risk of pneumonia, which became a 30% decreased risk after adjusting for comorbidities (adjusted odds ratio = 0.70, 95% CI = 0.46 to 0.65), and a 32% decreased risk after further adjusting for other confounders (adjusted odds ratio = 0.68, 95% CI = 0.63 to 0.73).

Eighty-seven per cent of statin users with prescriptions issued in the last 28 days had prescriptions for the two most common

Table 1. Characteristics of all cases with pneumonia and their matched controls at index date, and odds ratios for pneumonia associated with these characteristics

	Cases, *n* (%), *n* = 17 755	Controls, *n* (%), *n* = 80 484	Adjusted odds ratio (95% CI)[a]
Sex			
Male	8638 (48.7)	39 250 (48.8)	
Female	9117 (51.3)	41 234 (51.2)	
Age band, years			
45–54	2189 (12.3)	10 044 (12.5)	
55–64	2898 (16.3)	13 407 (16.7)	
65–74	3705 (20.9)	17 464 (21.7)	
75–84	5309 (29.9)	24 789 (30.8)	
≥85	3654 (20.6)	14 780 (18.4)	
Townsend deprivation score			
Quintile 1, most affluent	3472 (19.6)	17 371 (21.6)	1.00 (reference)
Quintile 2	3466 (19.5)	16 977 (21.1)	1.00 (0.95 to 1.06)
Quintile 3	3573 (20.1)	16 064 (20.0)	1.07 (1.01 to 1.13)
Quintile 4	3364 (18.9)	14 024 (17.4)	1.13 (1.06 to 1.20)
Quintile 5, most deprived	3460 (19.5)	13 602 (16.9)	1.21 (1.14 to 1.30)
Townsend score missing	420 (2.4)	2446 (3.0)	
Smoking status			
Non-smoker	10 858 (61.2)	52 207 (64.9)	1.00 (reference)
Current smoker	4006 (22.6)	12 287 (15.3)	1.57 (1.50 to 1.64)
Not recorded	2891 (16.3)	15 990 (19.9)	
Comorbidities			
Diabetes	1959 (11.0)	6144 (7.6)	1.33 (1.26 to 1.41)
Chronic heart disease	5265 (29.7)	14 357 (17.8)	1.66 (1.59 to 1.73)
Chronic renal disease	313 (1.8)	599 (0.7)	1.78 (1.53 to 2.07)
Chronic respiratory disease	5406 (30.4)	11 337 (14.1)	2.47 (2.37 to 2.58)
Chronic liver disease	136 (0.8)	262 (0.3)	1.85 (1.48 to 2.31)
Sickle cell or coeliac disease	55 (0.3)	138 (0.2)	1.72 (1.23 to 2.39)
HIV/AIDS	15 (0.1)	10 (0.0)	5.90 (2.55 to 13.64)
Immunosuppressed	2677 (15.1)	8385 (10.4)	1.22 (1.13 to 1.32)
Stroke or transient ischaemic attack	2403 (13.5)	6095 (7.6)	1.68 (1.58 to 1.77)
Rheumatoid arthritis	592 (3.3)	1297 (1.6)	1.83 (1.64 to 2.03)
Parkinson's disease	393 (2.2)	850 (1.1)	1.98 (1.74 to 2.26)
Multiple sclerosis	126 (0.7)	173 (0.2)	3.84 (3.02 to 4.89)
Dementia	729 (4.1)	1300 (1.6)	2.68 (2.42 to 2.97)
Osteoporosis	927 (5.2)	2507 (3.1)	1.42 (1.30 to 1.55)
Cancer	1723 (9.7)	4851 (6.0)	1.36 (1.24 to 1.49)
Medications/vaccinations, in previous 12 months			
Acid-lowering drugs	9399 (52.9)	37 727 (46.9)	1.41 (1.36 to 1.47)
Influenza vaccination	1079 (6.1)	4805 (6.0)	1.05 (1.00 to 1.09)
Pneumococcal vaccination	6490 (36.6)	20 365 (25.3)	0.90 (0.83 to 0.98)

[a]*Odds ratios refer to multivariate analysis investigating the effect of the confounders to pneumonia risk. Cases and controls were matched by age and sex, so odds ratios were not calculated for these variables.*

statins: atorvastatin (35%) and simvastatin (52%). These two statins had similar associations with the risk of pneumonia, with a 30% decrease for current users of simvastatin and atorvastatin (adjusted odds ratios = 0.70, 95% CI = 0.63 to 0.77, and 0.70, 95% CI = 0.62 to 0.78 respectively).

Individuals in the subgroup of cases diagnosed with lobar and pneumococcal pneumonia were slightly younger (median age 72 years, interquartile range 61–81 years) and more likely to be smokers (24.6%) and diagnosed with chronic respiratory disease (32.4%) than the remaining cases. Table 3 shows the results of the analyses on these cases and their matched controls. Statin exposure in the year prior to the index date was not significantly associated with lobar and pneumococcal pneumonia risk (adjusted odds ratio = 0.92, 95% CI = 0.81 to 1.04) but current exposure with the last prescription within 28 days was associated with a 24% decreased risk of pneumonia (adjusted odds ratio = 0.76, 95% CI = 0.65 to 0.89). Exposure to different types of statins in the last year did not show an association with risk of lobar and pneumococcal pneumonia, but patients with current exposure to simvastatin (prescriptions in the last 28 days) had a significantly decreased risk of lobar and pneumococcal pneumonia (adjusted odds ratios = 0.75, 95% CI = 0.62 to 0.92). There was no significant association between current exposure to atorvastatin and pneumonia risk (adjusted odds ratio = 0.89, 95% CI = 0.71 to 1.12).

Analysis repeated on patients with complete data for smoking status and deprivation score showed similar results (available from authors). Analysis repeated excluding immunosuppressed patients and those diagnosed with cancer, HIV, or chronic kidney disease showed a 19% decreased risk of pneumonia associated with statin prescriptions in the year prior to the index date, after adjusting for confounding factors (adjusted odds ratio = 0.81, 95% CI = 0.76 to 0.87) and a 30% decreased risk (adjusted odds ratio = 0.70, 95% CI = 0.64 to 0.76) associated with current use.

DISCUSSION

Summary

In this large study based on the general population, it was found that exposure to statins is associated with a decreased risk of pneumonia. The effect was particularly marked in patients who had their last prescription for statins in the 28 days before the index date. Atorvastatin and simvastatin had similar associations.

The reduced risk of pneumonia associated with statin use would be equivalent to an absolute risk reduction of four cases per 10 000 patients aged 45 years and older treated over one year, and hence a number needed to treat (NNT) of 2500 assuming a causal association. This NNT value is high for the general population but would be lower in groups at increased risk of pneumonia, such as older people with comorbidities.

The study findings are comparable with a similar study on The Health Improvement Network, another population-based UK

Table 2. Odds ratios for pneumonia associated with exposure to statins in the year before the index date in all cases and controls

	Cases, *n* (%), *n* = 17 775	Controls, *n* (%), *n* = 80 484	Unadjusted odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Any statin				
Exposed in the last year	2231 (12.6)	8759 (10.9)	1.24 (1.18 to 1.31)	0.78 (0.74 to 0.83)
No exposure	15 524 (87.4)	71 725 (89.1)	1.00 (reference)	1.00 (reference)
Current[b]	1222 (6.9)	5444 (6.8)	1.09 (1.02 to 1.17)	0.68 (0.63 to 0.73)
Recent[c]	819 (4.6)	2669 (3.3)	1.49 (1.37 to 1.62)	0.97 (0.88 to 1.06)
Former[d]	190 (1.1)	646 (0.8)	1.41 (1.20 to 1.67)	0.89 (0.75 to 1.06)
Prescriptions for individual statins in the last year				
Atorvastatin	823 (4.6)	3341 (4.2)	1.16 (1.07 to 1.26)	0.79 (0.72 to 0.86)
Simvastatin	1222 (6.9)	4659 (5.8)	1.26 (1.18 to 1.35)	0.82 (0.76 to 0.88)
Pravastatin	210 (1.2)	832 (1.0)	1.18 (1.01 to 1.38)	0.80 (0.68 to 0.94)
Cerivastatin	44 (0.2)	178 (0.2)	1.06 (0.76 to 1.49)	0.92 (0.65 to 1.31)
Fluvastatin	79 (0.4)	344 (0.4)	1.05 (0.82 to 1.36)	0.82 (0.63 to 1.07)
Rosuvastatin	26 (0.1)	105 (0.1)	1.08 (0.69 to 1.68)	0.93 (0.58 to 1.48)
Prescriptions for atorvastatin				
None	16 932 (95.4)	77 143 (95.8)	1.00 (reference)	1.00 (reference)
Current[b]	432 (2.4)	1942 (2.4)	1.06 (0.95 to 1.18)	0.70 (0.62 to 0.78)
Recent[c]	292 (1.6)	1036 (1.3)	1.34 (1.17 to 1.53)	0.89 (0.77 to 1.02)
Former[d]	99 (0.6)	363 (0.5)	1.22 (0.97 to 1.53)	0.98 (0.78 to 1.25)
Prescriptions for simvastatin				
None	16 533 (93.1)	75 825 (94.2)	1.00 (reference)	1.00 (reference)
Current[b]	649 (3.7)	2788 (3.5)	1.13 (1.03 to 1.23)	0.70 (0.63 to 0.77)
Recent[c]	442 (2.5)	1380 (1.7)	1.55 (1.38 to 1.73)	1.02 (0.91 to 1.15)
Former[d]	131 (0.7)	491 (0.6)	1.20 (0.98 to 1.46)	0.86 (0.70 to 1.06)

[a]Adjusted for comorbidities, deprivation, smoking status, acid-lowering drugs, and influenza and pneumococcal vaccinations. [b]Current use: last prescription within 28 days. [c]Recent use: last prescription in 29–89 days, [d]Former use: last prescription in 90 days or more before the index date.

Table 3. Odds ratios for pneumonia associated with exposure to statins in the year before the index date, restricted to cases diagnosed with lobar and pneumococcal pneumonia and their matched controls

	Cases, *n* (%), *n* = 4102	Controls, *n* (%), *n* = 18 625	Unadjusted odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Any statin				
Exposed in the last year	586 (14.3)	2127 (11.4)	1.36 (1.22 to 1.51)	0.92 (0.81 to 1.04)
No exposure	3516 (85.7)	16 498 (88.6)	1.00 (reference)	1.00 (reference)
Current[b]	310 (7.6)	1333 (7.2)	1.15 (1.01 to 1.32)	0.76 (0.65 to 0.89)
Recent[c]	221 (5.4)	631 (3.4)	1.72 (1.46 to 2.03)	1.19 (1.00 to 1.43)
Former[d]	55 (1.3)	163 (0.9)	1.64 (1.20 to 2.24)	1.16 (0.83 to 1.61)
Prescriptions for individual statins in the last year				
Atorvastatin	221 (5.4)	818 (4.4)	1.29 (1.10 to 1.51)	0.95 (0.79 to 1.13)
Simvastatin	332 (8.1)	1125 (6.0)	1.43 (1.25 to 1.64)	1.00 (0.86 to 1.15)
Pravastatin	51 (1.2)	222 (1.2)	1.04 (0.76 to 1.43)	0.73 (0.52 to 1.02)
Cerivastatin	15 (0.4)	58 (0.3)	1.08 (0.60 to 1.96)	0.97 (0.53 to 1.80)
Fluvastatin	20 (0.5)	72 (0.4)	1.26 (0.75 to 2.12)	0.96 (0.56 to 1.67)
Rosuvastatin	7 (0.2)	37 (0.2)	0.77 (0.34 to 1.77)	0.66 (0.28 to 1.59)
Prescriptions for atorvastatin				
None	3881 (94.6)	17 807 (95.6)	1.00 (reference)	1.00 (reference)
Current[b]	119 (2.9)	458 (2.5)	1.25 (1.01 to 1.55)	0.89 (0.71 to 1.12)
Recent[c]	69 (1.7)	258 (1.4)	1.27 (0.96 to 1.67)	0.90 (0.67 to 1.21)
Former[d]	33 (0.8)	102 (0.5)	1.42 (0.95 to 2.13)	1.20 (0.78 to 1.84)
Prescriptions for simvastatin				
None	3770 (91.9)	17 500 (94.0)	1.00 (reference)	1.00 (reference)
Current[b]	163 (4.0)	695 (3.7)	1.14 (0.95 to 1.37)	0.75 (0.62 to 0.92)
Recent[c]	128 (3.1)	306 (1.6)	2.05 (1.65 to 2.54)	1.44 (1.14 to 1.81)
Former[d]	41 (1.0)	124 (0.7)	1.47 (1.03 to 2.12)	1.18 (0.80 to 1.74)

[a]Adjusted for comorbidities, deprivation, smoking status, acid-lowering drugs, and influenza and pneumococcal vaccinations. [b]Current use: last prescription within 28 days. [c]Recent use: last prescription in 29–89 days, [d]Former use: last prescription in 90 days or more before the index date.

database, but showed a larger association for current statin exposure (reduction of 30% versus 22%).[28]

Strengths and limitations

Strengths of the study were its large size, representative population, and use of routinely collected data from general practices all over the UK. Although the data were not collected for research purposes, recording of clinical diagnoses has been shown to have good levels of accuracy and completeness in other UK general practice databases.[29,30] Possible causes of bias and confounding were considered in the study design and analysis. Matching on age, sex, index year, and general practice removed confounding by these factors. A possible higher statin prescription rate in people with lower social deprivation[31] was accounted for by adjusting for Townsend deprivation score. Prospective recording of the exposure data before the outcome occurred eliminated recall bias.

The study has some limitations. Although the data contain detailed information on drug prescriptions, this may not reflect actual use. However, there is no reason to think that any non-adherence would systematically differ between cases and controls. Another possible source of misclassification arises from statins (simvastatin 10 mg) having become available over the counter in May 2004 in the UK, which would affect mostly younger people who are not entitled to free prescriptions.[32] However, 80% of cases and 79% of controls were aged 60 years or older and therefore entitled to free prescribed medications, and for most of the study period statins were available only on prescription.

Another limitation was the high proportion of missing values for smoking status, but similar results were obtained from the analysis on observations with recorded data. Although the study adjusted for multiple comorbidities and presented sensitivity analysis excluding patients with particularly bad health with similar results, it was not possible to eliminate the effect of the 'healthier' statin user,[33] and there may be some residual confounding.

It should be acknowledged that many cases of pneumonia are unlikely to have recorded evidence of X-ray or microbiological confirmation of the diagnosis. This is a potential source of bias but this methodological approach is the only way to generate substantial numbers of cases for analysis. The analysis was repeated on a restricted group of cases with lobar and pneumococcal pneumonia diagnoses confirmed by X-ray or microbiological tests. The similarity of the results obtained from the main sample and from the restricted group, particularly for simvastatin, suggests that the main findings can be generalised.

Comparison with existing literature

The findings of this study are comparable to those of a similar study on another population-based database from the UK,[21] but showed an even larger association for current statin exposure (reduction of 30% versus 22%). A recent study by Dublin *et al*, which found some evidence of a slight increase in pneumonia risk associated with current statin use,[22] was conducted on members of a healthcare-delivery system in the US, who were likely to be wealthier and healthier than the general population in the UK. This difference in findings might at least partly be explained by differences in the case–control selection (their cases and controls were aged 65–94 years), calendar years, confounding variables, and the different definition of 'current' use in that study (at least two prescriptions within the 180 days before the index date).

The present study showed a similar association for the two most commonly prescribed statins, atorvastatin and simvastatin, with regard to the risk of pneumonia: something that no epidemiological study has previously investigated. Most earlier studies did not specify which types of statin were prescribed, and the only two that did were largely simvastatin based (62% and 76% respectively).[20,22]

Implications for research

In this large population-based case–control study, it was found, after adjusting for potential confounders, that current exposure to statins is associated with a decreased risk of pneumonia. The study showed comparable associations for the two most commonly prescribed statins: simvastatin and atorvastatin. Analysis repeated on a restricted group with more severe forms of pneumonia demonstrated similar results. Although the reduction of risk in patients prescribed statins in the last 28 days appeared to be clinically significant, further randomised controlled trials are necessary before recommending statins to patients with an increased risk of pneumonia.

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Ethical approval

This study was independently reviewed in accordance with the QResearch® agreement with Trent Research Ethics Committee.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

Julia Hippisley-Cox is codirector of QResearch (a not-for-profit organisation that is a joint partnership between the University of Nottingham and Egton Medical Information Systems (EMIS), the leading commercial supplier of IT for 60% of general practices in the UK), and director of ClinRisk, which produces software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to improve patient care. Carol Coupland is a consultant statistician for ClinRisk. This work and any views expressed within it are solely those of the authors and not of any affiliated bodies or organisations.

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